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Enteroviral Encephalitis in a Child With CNS Relapse of Burkitt Leukemia Treated With Rituximab

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Summary: A boy with central nervous system relapse of Burkitt leukemia developed fever and neurological symptoms and cognitive impairment. He had received multi-drug chemotherapy including rituximab. Enterovirus (EV) was detected in cerebrospinal fluid by polymerase chain reaction, and magnetic resonance imaging findings were consistent with viral infection. The patient was treated with intravenous immunoglobulin and within 1 month cleared his EV. Rituximab can cause a profound B-cell deficiency predisposing patients to infections including EV encephalitis. This is the first report of enteroviral encephalitis in a child undergoing treatment for lymphoma with rituximab and suggests the need to watch for this complication of therapy.

Key Words: Burkitt, rituximab, enterovirus, encephalitis

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BACKGROUND

Rituximab is a chimeric anti-CD20 monoclonal antibody and increasingly being used for the treatment of B-cell lymphoma, posttransplantation B-cell lymphoproliferative disorders and autoimmune cytopenia.[1,2] It has significantly improved the outcome of high-risk B-cell non-Hodgkin lymphoma in children and adolescents and is being incorporated alongside standard chemotherapeutics in the treatment of high-risk disease.[3]

Adult patients receiving rituximab have a modest increased risk of infections secondary to decreased B cell number and function.[4,5] Here we report the occurrence of enterovirus (EV) encephalitis in a child with relapsed Burkitt leukemia following rituximab therapy.

OBSERVATIONS

A 5-year-old boy presented with 4-week history of back pain, progressive pallor, and pancytopenia on peripheral blood examination. Bone marrow showed 97% infiltration with blasts. Immunophenotyping of blasts identified CD10, CD19, and CD22 more than 99%, surface immunoglobulin (Ig) M 99%, lambda 98%,cytoplasmic mu 96%, kappa 5%, tdt 1%, and CD34 < 1% expression. Cytogenetics confirmed IGH-MYC rearrangements by interphase fluorescence in situ hybridization. Blasts were also documented in the cerebrospinal fluid (CSF). No other cells were seen. At diagnosis, computed tomography and magnetic resonance imaging reported no systemic lymphoma masses. The patient was treated according to Inter-B-NHL 2010 Protocol, Group C3. The CSF was cleared of blasts after the first intrathecal chemotherapy.

Unusually from day 8 the CSF showed an increased white cell count (15 WBC/mm^3) with 26% lymphocytes, 62% neutrophils, and 12% monocytoid cells but no morphologic evidence of blasts on cytospin. Peripheral blood counts on day 8 revealed a hemoglobin 103 g/L, white blood cell count 1.1×10^9/L, neutrophil count 0.7×10^9/L, lymphocyte count 0.3×10^9/L, and platelets 91×10^9/L. Post R-COPADM1, the patient developed persistent fever unresponsive to antibacterial and antifungal treatment, with negative blood cultures and no localizing signs of infection on cross-sectional imaging. He received 2 doses of rituximab but the remaining drugs in COPDAM2 were delayed due to his clinical condition. Repeat CSF examination identified an isolated CNS relapse (on day 33 from commencement of the treatment). Immunophenotyping reported a 37% malignant population with CD22 and lambda expression > 96% and surface IgM 99%. No lymphoma masses were identified on cross-sectional imaging of the brain and spine. The bone marrow remained in remission. Treatment with rituximab, ifosfamide, carboplatin, etoposide, and dexamethasone (R-ICED) was commenced. CSF from same date detected EV by polymerase chain reaction but was reported negative for cytomegalovirus, herpes simplex virus 1 and 2, human herpes virus 6, Epstein-Barr virus, human parechovirus, and varicella zoster virus. In view of enteroviral infection intravenous immunoglobulin (IVIg) (0.5 g/kg/mo) was commenced. IgG levels at the time of leukemia diagnosis were in the normal range 5.17 g/L (4.9 to 16.1 g/L). The CSF was cleared of blasts after 2 intrathecal chemotherapy doses and prophylactic triple ITs were continued. However brfore second cycle of R-ICED, the patient again developed fever, recurrent focal seizures and a significant impairment of consciousness.

An electroencephalogram reported mild slow encepahlo-pathic background with no epileptic focus. Meningitic dose of IV meropenem, acyclovir and antiepileptic (levetiracetam) were commenced. Lumber puncture showed pleocytosis including neutrophils, lymphocytes, monocytes, and elevated protein (maximum 1.2 g/L). There was no morphologic or immunophenotypic evidence of Burkitt blasts. EV was again reconfirmed in the CSF by polymerase chain reaction and all other microbiological cultures remained negative on multiple occasions. One week later he had another episode of recurrent seizures followed by progressive alteration in cognitive functions associated with aphasia. On examination he had globally increased tone, brisk reflexes, decreased power, and upgoing planter. No focal neurological signs were noticed. Magnetic resonance

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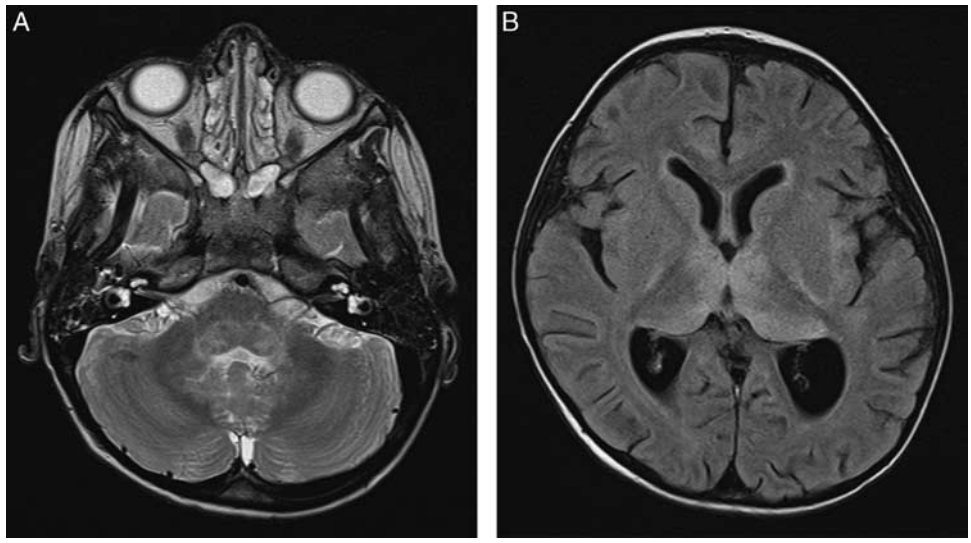

FIGURE 1. Magnetic resonance imaging showing T2 axial section (A) and FLAIR (B) axial sequences of the brain of 5-year-old boy with enterovirus encephalitis. Imaging reveal symmetrical high signal of the basal ganglia, brain stem and around fourth ventricle.

imaging of the head identified symmetrically high signals of bilateral basal ganglia, brain stem and around fourth ventricle, most consistent with viral encephalitis (Fig. 1). Alternative diagnoses including chemotherapy induced neurotoxicity and vitamin B_6 deficiency (B_6 level was 247 higher than normal range) were considered too.

The patient continued to be treated with weekly doses of IVIgs (0.5 g/kg). A repeat lumber puncture 1 month after the onset of neurological symptoms confirmed EV clearance of CSF. Unfortunately, the patient has continued to have significant neurological sequelae including impaired cognition, aphasia and movement disorders, despite remaining in leukemic remission.

CONCLUSIONS

Rituximab is recognized as standard agent in the treatment of pediatric high-risk B-cell lymphoma. On binding to CD20 it induces apoptosis and antibody dependent cellular cytotoxicity which leads to reduction in malignant blasts but also a rapid and long lasting depletion of circulating B cells. In the majority of patients this leads to no significant morbidities, and as such rituximab is seen as having a relatively good safety profile compared with standard chemotherapy. However in adults, several infectious side effects including hepatitis B reactivation, pneumocystis jirovecii pneumonia, progressive multifocal encephalopathy and EV meningoencephalitis have been reported.[6–10]

In the literature, 11 cases of EV meningoencephalitis are reported following rituximab therapy. In all rituximab was administered alongside immunosuppressive or cytotoxic drugs. Six patients were diagnosed with diffuse large B-cell lymphoma, 4 with follicular lymphoma and 1 with progressive marginal zone lymphoma. Among these only 1 patient is of pediatric age group diagnosed with severe idiopathic thrombocytopenic purpura. Because of the poor response he had multiple treatment modalities including 2 courses of rituximab infusions 6 months apart. Eleven months after the second course of rituximab infusions he presented with neurological impairment secondary to EV encephalitis. In all these patients the time interval between treatment with rituximab and neurological symptoms was variable (concurrent to 11 mo after completion) and patients died from EV meningoencephalitis, another infection or had only partial neurological improvement.[6,11–18]

EV are routinely neurotropic viruses. These viruses have the ability to enter into multiple CNS cell types including astrocytes, oligodendrocytes, microglial cells, neural progenitor, and stem cells thus enhancing their ability to persist and disseminate. Neurons may be more susceptible to EV infection due to the availability of specific internal ribosomal entry site trans-acting factors. The viral genome includes several cis-acting RNA which plays an important role in replication and/or translation. These viruses are highly cytolytic due to their ability to completely impair the host cells' translational machinery, thereby causing cytopathic effects. Viral protein 2B is a highly efficient viroporin which can permeablize the host cell membrane, as well as those of nearby cells. In addition EVs subvert the autophagic machinery to benefit their assembly, maturation and exit from host. EVs induce both antiapoptotic (3A and 2B proteins) and proapoptotic effects (VP2, 2A, and 3C proteins) on the host cell.[2] Neutralizing antibodies are thought to play a significant role in limiting EV infections. Hypogamma-globulinemic conditions increases the susceptibility to EV infections of CNS. Enteroviral genetic material can remain latent for a long time and in the presence of hypogammaglobuinemia may be reactivated and spread unchecked.[19]

Only few cases of rituximab associated EV encephalitis in adults with B-cell lymphoma have been reported, most with a grim outcome. The use of IvIg since the early 1980s has virtually eradicated EV meningoencephalitis in patients with congenital agammaglobulinemias. To our knowledge, this is the first report of EV encephalitis in a child with B-cell lymphoma. Our case illustrates that clinical symptoms and radiological abnormalities for EV encephalitis are non specific, especially in immunocompromised patients, leading to diagnostic difficulties. During early presentation, detection of viral RNA in the CSF may be falsely negative, due to low viral load. In this case the immunosuppressive effect of myelosuppressive chemotherapy may also have contributed to slow viral clearance.

Current treatment strategies involve the use of weekly immunoglobulins. The IVIg-based therapy, in addition to other inflammatory mechanisms might neutralize the circulating infectious virus within the host by passive immunization.[20] IVIG has also been administered intraventricularly, via Ommaya reservoir, with mixed clinical responses.[21] Although antiviral therapies like pleconaril and ribavirin have been shown to have some preclinical activity none are licensed for this indication. Ribavirin is a nucleoside analog and has been shown to inhibit the replication of a variety of EVs. Ribavirin acts by generating a highly, variable, noninfectious quasispecies and causing lethal mutagenesis. However, there are conflicting reports on the ability of ribavirin to cross the blood-brain barrier.[22] In addition, resistance against ribavirin is also reported. Pleconaril is another antiviral agent, that has the ability to cross the blood-brain barrier and remain within the CNS at concentrations that inhibit EV replication.[23] Pleconaril acts by inhibiting both viral attachment to the cognate receptor and uncoating of the nucleocapsid during replication. Studies have demonstrated that Pleconaril may be a valuable compound in the treatment of some EV infections of the CNS but resistance is also documented in some reports. Other nonapproaches such as rupintrivir and 17-AAG are undergoing preclinical testing.[24] With the increasing use of rituximab in children, a high index of suspicion is required in the development of unusual fevers or neurological signs. The development of a screening strategy for EV infections, sequential measurement of B cell and IgG concentrations and use of prophylactic Immunoglobulin in children who are receiving rituximab should be considered.

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